UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,697	02/10/2004	Richard A. Couch	PHARMA-148	7361

24999 7590 03/10/2006

MILLEN, WHITE, ZELANO & BRANIGAN, PC
2200 CLARENDON BLVD
SUITE 1400
ARLINGTON, VA 22201

EXAMINER	
ROYDS, LESLIE A	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 03/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/774,697	COUCH ET AL.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☒ Claim(s) *28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-28 are presented for examination.

Applicant's Amendment filed December 5, 2005 has been received and entered into the application. Accordingly, the specification at pages 1, 5, 6, 32, 34, 35, 36 and 39 has been amended and claims 1, 16, 20 and 28 are currently amended.

It is noted that Applicant has set forth amendments to the specification for the paragraph starting on page 36, line 1, which begins, "Amphetamines having l/d-isomer ratios...." at page 5 of the Amendment filed December 5, 2005. However, the referenced page number is in error. The paragraph to be amended begins at page 35, line 1.

In view of the amendments and remarks made herein, the objections to the claims; the objections to the specification, excluding the objection regarding browser-executable code at page 32, line 23 of the specification; the rejection of claims 1-15 and 22-26 under 35 U.S.C. 112, second paragraph, for omitting essential elements; the rejection of claims 4, 10 and 12 under 35 U.S.C. 112, second paragraph, for use of the term "about"; the rejections of claims 1-15 and 27-28 under 35 U.S.C. 102(b); and the rejection of claims 1-28 under 35 U.S.C. 103(a) as set forth at pages 2-15 of the previous Office Action dated June 6, 2005 have each been hereby **withdrawn**.

In view of the amendments to the claims, the rejection of claims 1-15 and 22-26 under the judicially created doctrine of obviousness-type double patenting over the composition claims of U.S. Patent Nos. 6,605,300 and 6,322,819 and the provisional rejections over the composition claims of U.S. Patent Application Nos. 11/091,011; 10/758,417; 10/433,151; 11/030,174; 10/673,557; and 10/353,073, as set forth at pages 15-17 of the previous Office Action dated June

6, 2005; and the provisional rejection of claims 16-21 over the method claims of U.S. Patent Application Nos. 11/030,174; 10/673,557; and 10/353,073, as set forth at pages 17-18 of the previous Office Action dated June 6, 2005, have each been hereby **withdrawn**. The provisional and non-provisional double patenting rejections have been withdrawn since the copending claims and the patented claims of the cited U.S. Patents and U.S. Patent Applications do not contain subject matter that would anticipate or render obvious under the doctrine of obviousness-type double patenting the present claims that are directed to a pharmaceutical combination with the recited release profile and characteristics.

Objection to the Claims (New Ground of Objection)

Claim 28 is objected to for reciting the phrase "said inattentiveness later in the day", which lacks antecedent basis in the claims.

Objection to the Specification

Applicant's removal of the hyperlink at page 32, line 16 of the specification has been noted. However, insofar as Applicant has failed to remove the hyperlink from the specification at page 32, line 23, the objection remains proper.

The disclosure remains objected to because it contains an embedded hyperlink and/or other form of browser-executable code at page 32, line 23. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP §608.01.

Objections to the Specification (New Ground of Objection)

Applicant's amendment to the specification at page 6, line 14 and page 6, line 4 from the bottom of the page has been noted. However, it has been further noted that the amendment to the trademark ADDERALL® in the paragraph beginning on page 6, line 14 is inadvertently in error. The specification as originally filed stated ADDERALL XR®, not ADDERALL®, at this line of the paragraph. The same error has occurred at line 1 of the paragraph beginning at page 6, line 4 from the bottom of the page. The specification as originally filed stated ADDERALL XR®, not ADDERALL® at this line of the paragraph. Applicant is requested to amend the specification to be consistent with the text of the specification as originally filed.

Claim Rejection - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20 and 25 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention, for the reasons already made of record at pages 6-7 of the previous Office Action dated June 6, 2005.

Applicant references a plethora of case law that held the term "about" as not indefinite (see, *Modine Mfg. Co. v. U.S. Intern. Trade Comm'n*, 75 F.3d 1545, 1554 [37 USPQ2d 1609] (Fed. Cir. 1996), etc. cited at page 13 of Applicant's remarks). Applicant relies on the statement that "about" is not broad or arbitrary but rather is a flexible term with a meaning similar to

'approximately' in support of their position and submits that one of ordinary skill in the art would understand the scope of the claims.

Applicant's amendments and remarks have each been carefully considered in their entirety, but fail to be persuasive in establishing error in the propriety of the present rejection.

Rejection of claims 20 and 25 remains proper because claims 20 and 25 each recite "greater than abut 1:1 or contains l isomer only" (see line 4 of each of claims 20 and 25). It remains that the scope of the claim is indefinite because Applicant has not made clear which is meant to be the limiting term, i.e., whether the range is limited by the phrase "greater than" or "about". For example, the recitation of "greater than" indicates that the ratio is greater than 1:1, but the recitation of the term "about" indicates that there is some amount of acceptable variation either above or below the given ratio. Thus, the use of the two terms together does not make clear that which is the ratio amount(s) that Applicant intends to claim. For these reasons, it remains that one of ordinary skill in the art would not be reasonably apprised of the scope of the invention and, as a result, the public would not be informed of the boundaries of what constitutes infringement of the present claims.

Rejection of claims 20 and 25 remains proper and is **maintained**.

Claim Rejection - 35 USC § 103 (New Ground of Rejection)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary

skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Patrick et al. ("Pharmacology of Methylphenidate, Amphetamine Enantiomers and Pemoline in Attention-Deficit Hyperactivity Disorder", 1997; p.527-546) in view of Hartmann et al. ("Sleep: Effects of d- and l-amphetamine in Man and in Rat; *Psychopharmacology*, 1976; p.171-175), Epstein et al. (WO 02/039998; May 23, 2002, already of record), Drug Facts and Comparisons (1996; 1230-1233) and Remington's Pharmaceutical Sciences (Sixteenth Edition, 1980; p.1594-1602).

Patrick et al. teaches dextroamphetamine and levoamphetamine mixed salts, marketed and sold under the brand name ADDERALL in the treatment of attention-deficit hyperactivity disorder (ADHD; page 537, col.2, last 2 paragraphs). Patrick et al. discloses that ADDERALL is a combination product comprising dextroamphetamine saccharate, dextroamphetamine sulfate, racemic amphetamine aspartate and racemic amphetamine sulfate (page 537, col.2, last paragraph). Patrick et al. also teaches that the total free base equivalence in, for example, a 10 mg tablet is 6.3 mg, of which 81% is dextroamphetamine and 19% is levoamphetamine (see also page 537, col.2, last paragraph).

The differences between the Patrick et al. reference and the presently claimed subject matter lie in that the reference fails to teach:

(i) a pharmaceutical combination wherein the molar ratio of l-amphetamine to d-amphetamine released from the combination later in the day is higher than said ratio released therefrom in a time period earlier in the day and the use of such a composition to treat ADHD or inattentiveness in an ADHD human patient;

(ii) the particularly claimed molar ratios of d-amphetamine to l-amphetamine (or vice versa) or the total amphetamine dose per day; or

(iii) the use of a single dosage form comprising d- and l-amphetamine with the presently claimed release profile or two separate dosage forms, one comprising d-amphetamine alone or in greater quantity than l-amphetamine and one comprising l-amphetamine alone or in greater quantity than d-amphetamine, either of which can be formulated as single staged-release, immediate release, pulse release and/or sustained or controlled release dosage forms.

However, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because combination products of dextroamphetamine and levoamphetamine mixed salts, such as ADDERALL, were known and commonly used in the art for the treatment of patients with attention-deficit hyperactivity disorder (see Patrick et al., pages 536-538). As Patrick et al. teaches, ADDERALL was known to be comprised primarily of dextroamphetamine and was known to exhibit similar side effects to that of dextroamphetamine alone (see page 537, col.2, last paragraph, and page 538, col.1, "Side-effects"), such as insomnia, anorexia, weight loss,

irritability, abdominal pain or headache (page 537, col.1, third paragraph). While Patrick et al. states that dextroamphetamine produced more pronounced psychopharmacological effects than the (-)-isomer, he also states that dextroamphetamine produced more pronounced peripheral sympathomimetic side-effects than levoamphetamine (page 536, col.2, first paragraph).

In this regard, Hartmann et al. ("Sleep: Effects of d- and l-amphetamine in Man and in Rat; *Psychopharmacology*, 1976; p.171-175) is cited. Hartmann et al. teaches, "It is widely recognized that in general the amphetamines produce cortical arousal or activation and that they promote wakefulness in man at times of drowsiness or sleep deprivation. The dextro-isomer (d-amphetamine) has usually been found to be more potent in these regards than the levo-isomer (l-amphetamine)." (col.1, page 171, first paragraph following abstract) Hartmann et al. demonstrated that waking was increased by d-amphetamine but not by l-amphetamine in both humans and rats (see col.1, page 172, first paragraph following "Results").

However, there were some known advantages to the use of l-amphetamine as the primary agent. Epstein et al. (WO 02/039998; May 23, 2002) is cited to show that the (-)-isomer (i.e., levoamphetamine) showed more potent memory enhancing effects that the (+)-isomer (i.e., dextroamphetamine) and was also not found to be addictive. Epstein et al. teaches, "In particular, we describe herein the use of pharmaceutical preparations for increasing long-term potentiation and/or improving long-term memory in animals, such as humans, which include R-(-)-amphetamine or a derivative thereof. R-(-)-amphetamine is at least 4 times more effective as a memory enhancer as compared to the commonly prescribed S-(+)-enantiomer of amphetamine. In addition, unlike S-(+)-amphetamine, the R-(-) enantiomer has not been shown to be addictive (page 26, lines 26-32)."

Thus, while the l-isomer of amphetamine was known to have fewer peripheral sympathomimetic side effects than the d-isomer, it was known in the art that it did not have as great an effect on maintaining wakefulness as the d-isomer of amphetamine. An ideal regimen for the treatment of attention-deficit hyperactivity disorder and the inattentiveness that is associated with such a condition would balance an effective amount of stimulant(s) sufficient to enhance alertness, memory and wakefulness during the day, while minimizing the side effects that result from such a treatment, such as insomnia, anorexia, weight loss, irritability, addiction, etc. However, given what was known independently about pharmaceuticals composed primarily of d-isomer and those composed primarily of l-isomer, it would have been *prima facie* obvious to one of ordinary skill in the art to combine both d-isomer and l-isomer in such a way as to enhance wakefulness and memory during the day but to minimize the effects that such stimulants have on disturbing sleep patterns.

The skilled artisan would have recognized that alertness and enhanced memory function would have been essential for normal function during the course of the day. Typically, pharmaceutical therapies, such as agents enriched with d-isomer, were well known in the art and used commonly for maintaining such function. However, the untoward effects of d-isomer on sleep patterns discouraged use prior to sleep in order to avoid insomnia (see Drug Facts and Comparisons; p.1232). As a result, it was harder to maintain a therapeutic level of amphetamine in the body over the entire course of the day, of which a less than therapeutic level of amphetamine would result in the manifestation of ADHD symptoms, thereby affecting normal function and precluding the performance of activities that require alertness, wakefulness, attention and enhanced memory.

However, in light of the fact that the l-isomer had significantly more potent activity as a memory enhancer than d-isomer, and further in light of the fact that l-isomer had significantly less, if any, effect on promoting wakefulness than d-isomer, it would have been *prima facie* obvious to one of ordinary skill in the art to employ a combination pharmaceutical regimen, wherein primarily d-isomer (i.e., either exclusively d-isomer or d-isomer in combination with l-isomer, wherein more d-isomer than l-isomer was present) was administered in the morning in a dose sufficient to maintain alertness, wakefulness and memory function for a major portion of the day, and then to consequently administer l-isomer (i.e., either exclusively l-isomer or l-isomer in combination with d-isomer, wherein more l-isomer than d-isomer was present) was administered later in the afternoon or evening in a dose sufficient to maintain enhanced memory function while avoiding extended wakefulness that disturbs normal sleep patterns. Such a person would have been motivated to do so in order to maintain alertness, wakefulness, attention and enhanced memory function for the entire, or almost the entire, day, but to minimize the disruptive effect of stimulant therapy on sleep patterns, which not only interferes with achieving an adequate amount of sleep for normal function, but also exacerbates the symptoms associated with ADHD, such as memory loss, insomnia, inability to pay attention, etc. due to a lack of adequate rest.

Furthermore, there is no reason to doubt that such a combination therapy would have been equivalent to, or superior than, the efficacy demonstrated by the same amount of d-amphetamine, since it would have been *prima facie* obvious to the skilled artisan that such a combination therapy of d-isomer and l-isomer would have necessarily had fewer effects on sleep deterioration and decreased food intake because the very nature of administration of l-isomer

was well known in the art to have fewer side effects that the d-isomer (see Patrick et al., cited above).

In addition, it would have been well within the purview of the skilled artisan to employ such a combination therapy described above as one single dosage form or two separate dosage forms each formulated such that more d-isomer than l-isomer was released immediately following administration and the release of l-isomer was delayed such that the latter portion of the therapeutic effect was attributable to a greater release of l-isomer than d-isomer. Various methods of release known in the art would have been acceptable means by which to achieve such differing release profiles, such as immediate, pulsed, controlled or sustained release (see Remington's Pharmaceutical Sciences, 1980; pages 1594-1602).

Lastly, the determination of the optimum molar ratios by which to achieve such a therapeutic regimen or the optimum total dosage amount per day to treat ADHD with the presently claimed active agent(s) would have been a matter well within the purview of one of ordinary skill in the art. Such a determination would have been made in accordance with a variety of factors, such as the age, weight, sex, diet and medical condition of the patient, severity of the disease, the route of administration, pharmacological considerations, such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the molar ratios or total dosage amount per day that would have actually been employed would have varied widely and, in the absence of evidence to the contrary, the currently claimed ratios or total dosage amount per day are not seen to be inconsistent with those that would have been determined by the skilled artisan.

Applicant's attention is drawn to MPEP at §2144.05, which states, "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages...Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Although the present sets of facts are drawn to molar ratios or mg/day amounts, such a motivation as cited from the MPEP at §2144.05 is nonetheless relevant.

Conclusion

Rejection of claims 1-28 is proper.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (8:30 AM-5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571)-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Leslie A. Royds
Patent Examiner
Art Unit 1614

March 6, 2006

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600